Clinical Abstract

Prophylactic Use of Bone Cements with Antibiotics in Primary Arthroplasty

The development of antibiotic bone cements goes back to Buchholz and Engelbrecht, who were the first to report on the possibility of adding antibiotics to bone cement in 1970 (1). The use of polymethyl methacrylate bone cements containing antibiotics as part of a local release system is well established as an effective method for prophylaxis of infections in the bone. The use of antibiotic bone cements in primary arthroplasty has spread globally.

Infection after a joint replacement is a serious and feared complication in orthopaedics. It causes discomfort, severely limits patient mobility and generally requires further surgical intervention. The infection rate after the first implantation of hip or knee arthroplasty is currently indicated at 1.2-4% (2, 3), whereby infections after a knee arthroplasty has been implanted are more frequent than following implantation of a hip arthroplasty (4).

Picture 1. Schematic representation of a cemented hip endoprosthesis

Risk factors that may cause a postoperative infection following a joint replacement include (5):

- Presence of an inflammatory joint disease, e.g. rheumatoid arthritis
- Immunosuppression caused by diseases like diabetes mellitus, drugs or irradiation
- Earlier infection of a joint
- Malnutrition
- Haemophilia
- Being overweight

The risk of infection for hip and knee implants is decidedly higher in revision surgery than primary interventions. Antibiotic bone cements are used for infection prophylaxis in both revision surgery and primary arthroplasty. Along with improved surgical techniques, optimised perioperative preparation and hygiene as well as systemic antibiosis, they are a fundamental component for reducing infection rates (5). The reduced infection rate under local antibiotic prophylaxis in primary arthroplasty can be explained by direct prevention of biofilm formation of bacteria on the implant (6). Aseptic prosthetic loosening is the most common reason for a revision, but chronic infections regarded as low-grade or minimal are increasingly being recognised as a cause of loosening diagnosed as aseptic (7). A not insignificant argument for this is the reduction in rates of aseptic loosening with combined local and systemic antibiosis (8).

Antibiotic Bone Cement as the Local Drug Vehicle

Every implanted biomaterial is susceptible to bacterial colonisation on the surface; bacteria can elude the body's natural defences and spread (9). Local use of antibiotics can prevent the formation of a bacterial biofilm and a subsequent haematogenous infection (10). Antibiotic bone cements offer short to medium-term protection from periprosthetic infections (11). They are a local drug vehicle in which the bone cement acts as a carrier matrix. Antibiotic bone cements are superior to a systemic antibiotic prophylaxis due to higher local active material concentrations (12). Especially in those parts of the bones and joints that are difficult to access, local application offers advantages over systemic application (13). This reduces the risk of infection-related revision (10). Bone cements with a lower antibiotic content are used for infection prophylaxis in primary arthroplasty and revision surgery. A combination of local and systemic antibiotic application has become the standard here (8, 10, 14, 15).

The vulnerable 6-hour phase immediately following insertion of a prosthesis is important for preventing bacterial colonisation and thus crucial for the implant's long-term success (16). A high initial release rate of the antibiotic from the bone cement is therefore desirable.

Properties of Bone Cement and Antibiotic

The release kinetics of the antibiotic from the cement are critical for effectiveness. The maximum release occurs in the first 10 hours after the cemented prosthesis has been implanted, with approximately 30% elution of the antibiotic (17). How well the antibiotic is released depends on both the antibiotic itself and the wettability, permeability and roughness of the bone cement (18). The release of surface effects play an important role here, especially in the first phase (6) (Tab. 1). When the release starts, the local antibiotic concentrations are 10-100 times greater than the values that can be achieved systemically (19).

Among other things, the mechanical properties of the set bone cement depend on the antibiotics added, the mixture and the homogeneity achieved by the cement as a result. Adding antibiotics in liquid form severely impairs the mechanical properties compared with an antibiotic in powder form, therefore it is not used. Adding antibiotic powder in a low concentration (up to 2g per 40g of cement) does not have a clinically relevant effect on the cement's mechanical properties and does not involve an increased prosthetic loosening rate. On the other hand, adding more than 10% antibiotic to bone cement decreases the mechanical properties (20). Bone cements with high antibiotic concentrations are therefore used specifically as temporary local drug vehicles, e.g. as spacers for treating an infection during a two-stage revision (22, 23). There are no clinical indications of systemic toxicity for antibiotic bone cement (24).

Industrially manufactured antibiotic bone cements are characterised by controlled high quality with unchanging material and processing properties. In these bone cements, the addition of antibiotics is highly standardised, which guarantees both good mechanical properties and high antibiotic release (18, 20). It must be ensured that the release rates from one and the same antibiotic differ for bone cements by different manufacturers because of the varying composition and manufacture (13).

Bone Cement	Antibiotic
▪ Good release of the antibiotic from the bone cement, depending on hydrophilia, permeability and roughness of the cement. ▪ The addition of antibiotics has the smallest possible influence on mechanical stability. ▪ Homogeneous mixture of cement due to the even distribution of crystalline antibiotic in polymer powder.	▪ Good water solubility and high initial release rate ▪ Broad antibacterial spectrum efficacy ▪ Bactericidal effect in a low concentration ▪ Few primary clinically relevant resistant bacteria ▪ Low protein binding ▪ Low allergenic potential ▪ Low effect on the bone cement's stability ▪ Thermal stability ▪ No chemical reaction with the bone cement's components

Tab. 1. Physical, chemical and bacteriological requirements for the bone cement and antibiotic (18, 20, 21).

The ideal properties of an antibiotic for local infection prophylaxis are listed in Table 1. The most important of these are good water solubility, broad antibacterial spectrum efficacy and a bactericidal effect even at a low concentration. The antibiotic should be released quickly and in a high concentration and guarantee high local levels of efficacy. Moreover, the released dosage should be greater than the minimum inhibitory concentration and minimum bactericidal concentration of the particular pathogen (20).

Common Antibiotics for Bone Cements

Out of all available antibiotics, the aminoglycoside gentamicin has proved to be the best. Its effect has been evidenced in numerous studies (11, 25, 26). Furthermore, gentamicin performs well in view of the frequency of primary resistance. According to data from the study by the Working Group of Sensitivity Tests & Resistance at the Paul Ehrlich Society in 2004, the frequency of resistance for erythromycin and clindamycin is insignificant, but in tobramycin and especially gentamicin it has been in sharp decline since 2001 (27), even though use of these antibiotics is widespread.

Due to the use of antibiotic bone cement, which has become standard practice in many German hospitals and clinics, a clear reduction of the infection rate has been observed. Gentamicin has a wide antibacterial spectrum, which for bone infections includes particularly important Staphylococcus aureus strains and problematic gram-negative bacteria (28). Even bacteria classified as moderate or insensitive after standard antibiograms are still detected in many cases due to the high local active substance concentration (29, 30). Clindamycin, which is one of the lincosamides, is a sensible addition in revision surgery, as it shows synergetic effects when combined with gentamicin, especially with staphylococci, and thus increases the antibacterial effect. As a reserve antibiotic, the glycopeptide antibiotic vancomycin is one therapy option for known bacterial resistance, especially in methicillin-resistant Staphylococcus aureus strains (31, 32).

Significant Reduction of Infection Rates

Antibiotic bone cements have been successfully used for decades in Europe, especially Scandinavia and central Europe, in the implantation of hip and knee arthroplasties. Clinical studies show a clear reduction of infection rates when antibiotic bone cements are used. The Scandinavian arthroplasty registers currently provide the most reliable and up-to-date data. They prove the advantage of antibiotic bone cements as part of primary arthroplasty for infection prophylaxis (8, 10, 14). The increasing use of antibiotic bone cements in primary arthroplasty has proved to result in a reduction of infection and revision rates and is associated with prostheses lasting longer (8, 10, 14, 15).

A major meta-analysis by Parvizi et al., which included 19 studies of 36,033 hip revisions in 35,659 patients, showed an approximate 50% reduction of infection rates in primary hip arthroplasty when antibiotic bone cements were used (33) (Fig. 1). The rate of deep infections was significantly reduced from 2.3% to 1.2% (p = 0.001). However, the authors also made it clear that there is still a major lack of randomised, controlled and prospective studies.

The most effective method of infection prophylaxis proved to be a combination of local and systemic antibiosis on the day of surgery. This approach led to the implants lasting longer as a result of protection from aseptic prosthetic loosening (8, 10, 14) (Fig. 2).

Lower Infection Rates in Knee Arthroplasty

There is also data documenting the use of antibiotic bone cement in primary knee arthroplasty. Particularly in northern European countries like Scandinavia, Great Britain and Germany, the use of antibiotic bone cement has increasingly become a clinical standard (34). An evaluation of data from the Norwegian Knee Arthroplasty Register between 1994 and 2000 showed that 87% of 7174 registered primary knee arthroplasties were cemented. 93% of cemented prostheses were in turn anchored with bone cement containing antibiotics, especially gentamicin (35). According to data from the regional arthroplasty register in northwest England, 97.7% of surgeons used bone cement to anchor primary total knee arthroplasties, while 93.7% used antibiotic cement (36). Data from the Finnish and Australian knee arthroplasty registers prove a reduction of the infection or revision risk when antibiotic bone cement was used (37, 38). In a prospective randomised study, Chiu et al. compared the use of bone cement with and without antibiotics in the implantation of 340 new knee arthroplasties (39). While 3.1% of patients operated on without antibiotic bone cement developed an infection, there was not one single case of an infection in patients operated on with antibiotic bone cement (p = 0.0238).

Although the European data clearly proves the efficacy of antibiotic bone cements in primary arthroplasty, these cements are currently only allowed for two-stage revision surgery in the USA. But cements containing antibiotics are also being increasingly used there for primary arthroplasty (40, 41), especially in risk patients with, for example, immunosuppression, inflammatory joint diseases or who are overweight (26).

Citation	Lower	Upper	n (total)	p-value	Antibiotic	Non-antibiotic	Antibiotic cement	Non-antibiotic c.	Effect
Espehaug (1997)	0.158	0.634	10905	0.001	11/6043	28/4862			0.316
Josefsson (1990)	0.178	1.038	1409	0.053	7/711	16/698			0.430
Josefsson (1993)	0.290	1.564	1115	0.36	9/565	13/550			0.674
Liebermann (1994)	0.168	16.908	35	0.65	2/19	1/16			1.684
Lynch (1987)	0.020	1.779	303	0.10	1/194	3/109			0.187
Lynch (1987)	0.382	2.501	1075	0.96	7/424	11/651			0.977
McQueen (1987)	0.047	5.567	295	0.57	1/146	2/149			0.510
Random combined	**0.341**	**0.751**	**15127**	**0.001**	**38/8102**	**74/7035**			**0.506**

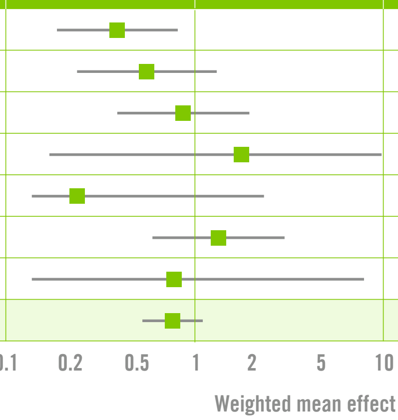


Fig. 1. Average reduction of infection risk as a result of antibiotic bone cement (with 95% confidence intervals) for primary hip arthroplasty. A value of <1 shows increasing efficacy with antibiotics, while a value of >1 indicates greater efficacy of bone cement without antibiotics (modified in accordance with (33)).

Potential Cost Reduction

Revision operations are associated with considerable costs. Various factors contribute to the high costs. These include the need for additional operations with multi-stage interventions or longer surgery times due to the often difficult local situation. Further costs often arise after the revision due to protracted rehabilitation measures, care dependency, chronic pain, but also the inability to work for a long period of time.

Local and systemic antibiotic therapy also contributes to lowering costs in primary interventions (42). Based on the approximately 50% lower infection rate (32) due to the use of bone cements containing antibiotics according to Parvizi et al. (32), the number of costly revisions and associated rehabilitation measures plus lingering prevention is reduced.

A study from the USA showed that the use of antibiotic bone cement in primary hip arthroplasty can lower the overall cost of the procedure, if both infection and aseptic loosening are regarded as a cause of the revision (43). The use of antibiotic bone cement initially involves additional costs, but this is counterbalanced by the reduction of infection-related complications and costs; this ultimately leads to clear savings (26, 44).

Resistance Created by Antibiotic Bone Cements?

As is the case for any treatment with antibiotics, the use of bone cement with added antibiotics may create resistance and selection of already resistant bacteria (25, 26). Sustained and repeated selection pressure with high bacterial density and a concurrent low antibiotic concentration in biofilms promotes the development of resistance (45, 46). However, there is no evidence of a connection between bacterial resistances and the routine application of antibiotic bone cement for infection prophylaxis in primary arthroplasty (47). An argument against the clinical relevance of potential development of resistance by antibiotic bone cements is the rate of infections with methicillin-resistant Staphylococcus aureus (MRSA) in Sweden (SENTRY Antimicrobial Surveillance Program), which is the lowest in Europe, even though antibiotic bone cements have been used there for decades (48). In Germany, especially the frequency of gentamicin-resistant bacteria, but also clindamycin-resistant bacteria, decreased from 2001–2004 despite the widespread clinical use of these antibiotics (27).

Unlike primary arthroplasty, the development of bacterial resistances plays an important role in revision surgery of infected implants (49, 50). Bone cements with combined antibiotics added like gentamycin and clindamycin (51) offer extra safety with their synergetic bactericidal efficacy. The wide bacterial spectrum with sensitivity to most pathogens detected in the course of periprosthetic infections and the much longer release of gentamicin from the bone cement with more effective inhibition of the bacterial biofilm are regarded as key advantages of a combination of these antibiotics (19). Moreover, the dual active antimicrobial principle contributes to reducing the development of resistances to gentamicin (52).

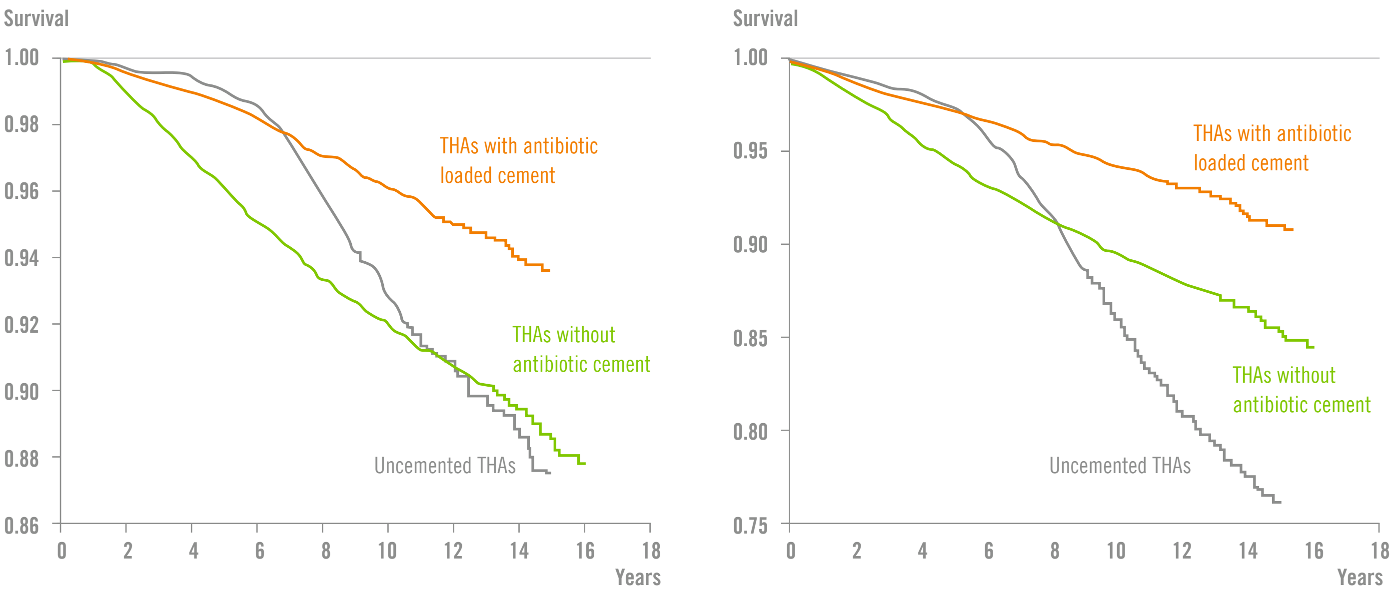


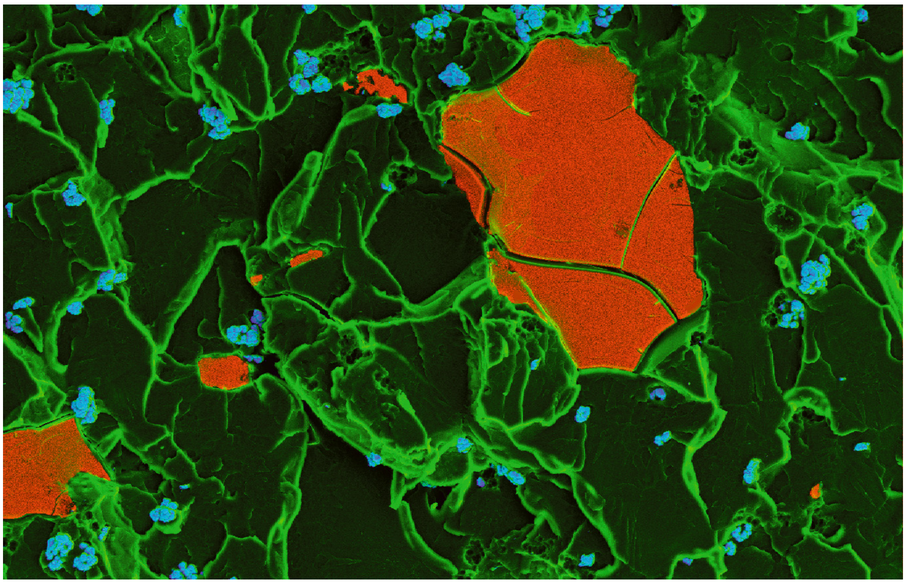
Fig. 2. The lowest rates of aseptic loosening (left) and revision of each cause (right) after primary hip joint replacement occur in patients for whom antibiotic-loaded bone cements were used; data from the Norwegian Arthroplasty Register of 2006 (n = 56,275) (8).

Conclusion

The use of bone cements containing antibiotics contributes to the reduction of periprosthetic infections in both primary arthroplasty and revision surgery. Moreover, a clear reduction of infection rates and longer endurance of prostheses could be proven in primary arthroplasty. Due to the avoidance of revision interventions, infection prophylaxis involves a cost saving and does not affect a patient's quality of life as much.

Adding low antibiotic concentrations does not adversely affect the mechanical properties of bone cements, and there are no clinical indications of toxic effects.
The use of antibiotic bone cements for infection prophylaxis in primary arthroplasty is also increasing internationally, due to the following factors:

- Antibiotic bone cements significantly reduce rates of infection
- The added antibiotics show broad spectrum efficacy with low primary resistance and do not affect the mechanical properties of bone cement in the course of infection prophylaxis
- Industrially manufactured antibiotic bone cements are available that guarantee high quality with constant material and processing properties
- There is no evidence for the appearance of bacterial resistances based on routine application of antibiotic bone cements.



Picture 2. PALACOS SEM picture® R+G SEM image PALACOS® R+G

Literature

1. Buchholz HW, Engelbrecht H. [Depot effects of various antibiotics mixed with Palacos resins]. Chirurg 1970; 41:511–515.
2. Knobben BA, Engelsma Y, Neut D, van der Mei HC, Busscher HJ, van Horn JR. Intraoperative contamination influences wound discharge and periprosthetic infection. Clin Orthop Relat Res 2006; 452:236–241.
3. Wodtke J, Lohr JF. [The infected implant]. Orthopade 2008; 37:257-267; quiz 268–269.
4. Hanssen AD, Rand JA. Evaluation and treatment of infection at the site of a total hip or knee arthroplasty. Instr Course Lect 1999; 48:111–122.
5. Jamsen E, Furnes O, Engesæter LB, et al. Prevention of deep infection in joint replacement surgery. Acta Orthop 2010; 81:660–666.
6. van de Belt H, Neut D, Schenk W, van Horn JR, van der Mei HC, Busscher HJ. Infection of orthopedic implants and the use of antibiotic-loaded bone cements. A review. Acta Orthop Scand 2001; 72:557–571.
7. Maathuis PG, Neut D, Busscher HJ, van der Mei HC, van Horn JR. Perioperative contamination in primary total hip arthroplasty. Clin Orthop Relat Res 2005;433:136–139.
8. Engesæter LB, Lie SA, Espehaug B, Furnes O, Vollset SE, Havelin LI. Antibiotic prophylaxis in total hip arthroplasty: effects of antibiotic prophylaxis systemically and in bone cement on the revision rate of 22,170 primary hip replacements followed 0–14 years in the Norwegian Arthroplasty Register. Acta Orthop Scand 2003; 74:644–651.
9. Gristina AG, Costerton JW. Bacterial adherence to biomaterials and tissue. The significance of its role in clinical sepsis. J Bone Joint Surg Am 1985; 67:264–273.
10. Espehaug B, Engesæter LB, Vollset SE, Havelin LI, Langeland N. Antibiotic prophylaxis in total hip arthroplasty. Review of 10,905 primary cemented total hip replacements reported to the Norwegian arthroplasty register, 1987 to 1995. J Bone Joint Surg Br 1997; 79:590–595.
11. Webb JC, Spencer RF. The role of polymethylmethacrylate bone cement in modern orthopaedic surgery. J Bone Joint Surg Br 2007; 89:851–857.
12. Josefsson G, Kolmert L. Prophylaxis with systematic antibiotics versus gentamicin bone cement in total hip arthroplasty. A ten-year survey of 1,688 hips. Clin Orthop Relat Res 1993; 292:210–214.
13. Wahlig H, Dingeldein E. Antibiotics and bone cements. Experimental and clinical long-term observations. Acta Orthop Scand 1980; 51:49–56.
14. Engesæter LB, Espehaug B, Lie SA, Furnes O, Havelin LI. Does cement increase the risk of infection in primary total hip arthroplasty? Revision rates in 56,275 cemented and uncemented primary THAs followed for 0–16 years in the Norwegian Arthroplasty Register. Acta Orthop 2006; 77:351–358.
15. Malchau H, Herberts P, Ahnfelt L. Prognosis of total hip replacement in Sweden. Follow-up of 92,675 operations performed 1978–1990. Acta Orthop Scand 1993; 64:497–506.
16. Poelstra KA, Barekzi NA, Rediske AM, Felts AG, Slunt JB, Grainger DW. Prophylactic treatment of gram-positive and gram-negative abdominal implant infections using locally delivered polyclonal antibodies. J Biomed Mater Res 2002; 60:206–215.
17. Trippel SB. Antibiotic-impregnated cement in total joint arthroplasty. J Bone Joint Surg Am 1986; 68:1297–1302.
18. Lewis G. Properties of antibiotic-loaded acrylic bone cements for use in cemented arthroplasties: a state-of-the-art review. J Biomed Mater Res B Appl Biomater 2009; 89B:558–574.
19. Gehrke T, v. Foerster G, Frommelt L, Marx A. Pharmacokinetic study of a gentamicin/clindamycin bone cement used in one-stage revision arthroplasty. In: Walenkamp GHIM, Murray DW, eds. Bone cements and cementing technique. Berlin: Springer 2001; 127–134.
20. Frommelt L, Kühn KD. Antibiotic-loaded cement. In: Breusch SJ, Malchau M, eds. The well-cemented total hip arthroplasty. Heidelberg: Springer 2005; 86–92.
21. van de Belt H, Neut D, Uges DR et al. Surface roughness, porosity and wettability of gentamicin-loaded bone cements and their antibiotic release. Biomaterials 2000; 21:1981–1987.
22. Duncan CP, Masri BA. The role of antibiotic-loaded cement in the treatment of an infection after a hip replacement. Instr Course Lect 1995; 44:305–313.
23. Springer BD, Lee GC, Osmon D, Haidukewych GJ, Hanssen AD, Jacofsky DJ. Systemic safety of high-dose antibiotic-loaded cement spacers after resection of an infected total knee arthroplasty. Clin Orthop Relat Res 2004; 427:47–51.
24. Jiranek W. Antibiotic-loaded cement in total hip replacement: current indications, efficacy, and complications. Orthopedics 2005; 28:s 873–877.
25. Hendriks JG, van Horn JR, van der Mei HC, Busscher HJ. Backgrounds of antibiotic-loaded bone cement and prosthesis-related infection. Biomaterials 2004; 25:545–556.
26. Jiranek WA, Hanssen AD, Greenwald AS. Antibiotic-loaded bone cement for infection prophylaxis in total joint replacement. J Bone Joint Surg Am 2006; 88:2487–2500.
27. Kresken M, Hafner D, Schmitz FJ, Wichelhaus TA, für die Studiengruppe PEG-Resistenzstudie. Resistenzsituation bei klinisch wichtigen Infektionserregern gegenüber Antibiotika in Deutschland und im mitteleuropäischen Raum. Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. 2004.
28. Wahlig H. Über die Freisetzungskinetik von Antibiotika aus Knochenzementen – Ergebnisse vergleichender Untersuchungen in vitro und in vivo. Chirurgie und Orthopädie 1987; 31:221–226.
29. Wahlig H, Buchholz HW. [Experimental and clinical studies on the release of gentamicin from bone cement]. Chirurg 1972; 43:441–445.
30. Buchholz HW, Gartmann HD. [Infection prevention and surgical management of deep insidious infection in total endoprosthesis]. Chirurg 1972; 43:446–453.
31. Scottish Intercollegiate Guidelines Network. Antibiotic prophylaxis in surgery. A national clinical guideline. Edinburgh 2008.
32. Frommelt L. Prinzipien der Antibiotikabehandlung bei periprothetischen Infektionen. Orthopäde 2004; 33:822–826.
33. Parvizi J, Saleh KJ, Ragland PS, Pour AE, Mont MA. Efficacy of antibiotic-impregnated cement in total hip replacement. Acta Orthop 2008; 79:335–341.
34. Bourne RB. Prophylactic use of antibiotic bone cement: an emerging standard – in the affirmative. J Arthroplasty 2004; 19:69–72.
35. Furnes O, Espehaug B, Lie SA, Vollset SE, Engesæter LB, Havelin LI. Early failures among 7,174 primary total knee replacements: a follow-up study from the Norwegian Arthroplasty

Register 1994–2000. Acta Orthop Scand 2002; 73:117–129.
36. Malik MH, Chougle A, Pradhan N, Gambhir AK, Porter ML. Primary total knee replacement: a comparison of a nationally agreed guide to best practice and current surgical technique as determined by the North West Regional Arthroplasty Register. Ann R Coll Surg Engl 2005; 87:117–122.
37. Jamsen E, Huhtala H, Puolakka T, Moilanen T. Risk factors for infection after knee arthroplasty. A register-based analysis of 43,149 cases. J Bone Joint Surg Am 2009; 91:38–47.
38. Australian Orthopaedic Association. National Joint Registry. Annual Report. Adelaide 2009.
39. Namba RS, Chen Y, Paxton EW, Slipchenko T, Fithian DC. Outcomes of routine use of antibiotic-loaded cement in primary total knee arthroplasty. J Arthroplasty 2009; 24:44–47.
40. Heck D, Rosenberg A, Schink-Ascani M, Garbus S, Kiewitt T. Use of antibiotic-impregnated cement during hip and knee arthroplasty in the United States. J Arthroplasty 1995; 10:470–475.
41. Bourne RB. Antibiotic bone cement approval: fuss-in at the Feds! Orthopedics 2002; 25:913–914.
42. Persson U, Persson M, Malchau H. The economics of preventing revisions in total hip replacement. Acta Orthop Scand 1999; 70:163–169.
43. Cummins JS, Tomek IM, Kantor SR, Furnes O, Engesæter LB, Finlayson SR. Cost-effectiveness of antibiotic-impregnated bone cement used in primary total hip arthroplasty. J Bone Joint Surg Am 2009; 91:634–641.
44. Randelli P, Evola FR, Cabitza P, Polli L, Denti M, Vaienti L. Prophylactic use of antibiotic-loaded bone cement in primary total knee replacement. Knee Surg Sports Traumatol Arthrosc 2010; 18:181–186.
45. Neut D, van Horn JR, van Kooten TG, van der Mei HC, Busscher HJ. Detection of biomaterial-associated infections in orthopaedic joint implants. Clin Orthop Relat Res 2003; 413:261–268.
46. van de Belt H, Neut D, Schenk W, van Horn JR, van der Mei HC, Busscher HJ. Gentamicin release from polymethylmethacrylate bone cements and Staphylococcus aureus biofilm formation. Acta Orthop Scand 2000; 71:625–629.
47. Dunbar MJ. Antibiotic bone cements: their use in routine primary total joint arthroplasty is justified. Orthopedics 2009; 32.
48. Sader H, Fritsche T, Stillwell M, Jones R. 10 years of surveillance of bloodstream infections in European medical centers by the SENTRY Antimicrobial Surveillance Program (1997–2006). 17th European Congress of Clinical Microbiology and Infectious Diseases, March 31–April 3, 2007, Munich.
49. Stefansdottir A, Johansson D, Knutson K, Lidgren L, Robertsson O. Microbiology of the infected knee arthroplasty: report from the Swedish Knee Arthroplasty Register on 426 surgically revised cases. Scand J Infect Dis 2009; 41:831–840.
50. Kilgus DJ, Howe DJ, Strang A. Results of periprosthetic hip and knee infections caused by resistant bacteria. Clin Orthop Relat Res 2002; 404:116–124.
51. Kühn K. Bone cements. Up-to-date comparison of physical and chemical properties of commercial materials. Berlin, Heidelberg, New York, Tokio: Springer 2000.
52. Ensing GT, van Horn JR, van der Mei HC, Busscher HJ, Neut D. Copal bone cement is more effective in preventing biofilm formation than Palacos R-G. Clin Orthop Relat Res 2008; 466:1492–1498.